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Filed : May 1, 2002

REMARKS

Claims 1-5 are pending for examination.

Utility

Claims 1-5 were rejected under 35 U.S.C. 101 on the assertion that they do not satisfy the utility requirement. The Examiner asserts that he has cited numerous pieces of art that show mRNA does not correlate with protein. In particular, the Examiner asserts that the Alberts and Lewin references actually support the Examiner's position in that they teach controls and at several levels these controls can have an effect on expression of the protein. According to the Examiner, while the art of Zhigang et al does show protein expression, the experiments were carried out to demonstrate this and as such Zhigang et al support that one needs to actually determine the expression of the protein in order to be sure of expression.

Gokman-Polar is cited as teaching the absence of any necessary correlation between increased mRNA levels and increased protein levels. Gygi is cited as teaching that correlation between mRNA and protein levels were insufficient to predict protein expression and that those that were correlated suggested an importance of posttranslational mechanisms controlling gene expression and that simple deduction from mRNA analysis is insufficient.

With respect to Applicants' previous arguments regarding Hu, the Examiner asserts that the arguments do not present any evidence that differences under 5 fold would be useful for diagnosis as asserted because the PRO1864 is only overexpressed 2 fold.

According to the Examiner, it is not necessarily the norm that gene expression, or even transcription, parallels protein expression.

Utility – Legal Standard

As previously noted, according to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

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The requirement of “substantial utility” defines a “real world” use, and derives from the Supreme Court’s holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that “The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility.” In explaining the “substantial utility” standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient*, at least with regard to defining a ‘substantial’ utility.” (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that “Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.” Further, “to violate § 101 the claimed device must be totally incapable of achieving a useful result.” *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), citing *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: “If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that “to overcome the presumption of truth that an assertion of utility by the applicant enjoys” the PTO must establish that it is “more likely than not that one of ordinary skill in the art would doubt (i.e., ‘question’) the truth of the statement of utility.” M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

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Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.** M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

As previously noted, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, “unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.” *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or “more likely than not” standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true “beyond a reasonable doubt.” **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence “that one of ordinary skill in the art would reasonably doubt the asserted utility.” *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

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In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

[T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be “*reasonably* indicative of the desired [pharmacological] response.” In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior.” *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art “to a reasonable probability.” In addition, the evidence need not be direct, so long as there is a “sufficient correlation” between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

[I]n *vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable

correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is “an invariable exact correlation” between gene expression and protein expression. Instead, Applicants’ position detailed below is that a measured change in gene expression in cancer cells establishes a “significant probability” that the expression of the encoded polypeptide in cancer will also be changed based on “a reasonable correlation therebetween.”

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.** The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants’ Arguments and the PTO’s Response

In an attempt to clarify Applicants’ argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic and therapeutic tools for cancer, particularly melanoma. Applicants’ asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1864 polypeptide is more highly expressed in melanoma compared to normal skin tissue;

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2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding change in the level of the encoded protein, e.g. an increase;

3. Given Applicants' evidence that the level of mRNA for the PRO1864 polypeptide is increased in melanoma compared to normal skin tissue, it is likely that the PRO1864 polypeptide is more highly expressed in melanoma compared to normal skin tissue;

4. Antibodies to proteins which are differentially expressed in certain tumors are useful as diagnostic and therapeutic tools.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the reliability of the evidence reported in Example 18, and states that it provides no information regarding protein expression;

2. The PTO asserts that it has provided numerous references which demonstrate that mRNA does not correlate with protein.

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B. First, the PTO has failed to offer any evidence to support its rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data. Second, Applicants submit that in general differential mRNA expression correlates with differential protein expression. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability**, that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Applicants have established that the Gene Encoding the PRO1864 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

The Examiner asserts that the Grimaldi declarations state that Example 18 showed mRNA expression but do not state that the protein was expressed.

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Applicants maintain that the data in Example 18 demonstrates that the mRNA encoding PRO1864 is more highly expressed in melanoma compared to normal skin tissue. In support of this position, Applicants have previously submitted a copy of a first declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest “can be used to differentiate tumor from normal.” He explains that, “The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue.” (Paragraph 7).

As Mr. Grimaldi states, “[i]f a difference is detected, this indicates that *the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes*, to screen samples to differentiate between normal and tumor.” (Paragraph 7, emphasis added). The data presented in Example 18 show that the gene encoding PRO1864 is more highly expressed in melanoma compared to normal skin tissue. As the Grimaldi declaration indicates, the disclosed gene and its corresponding polypeptide and antibodies are therefore useful as diagnostic tools.

Applicants submit that the declaration is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that “[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned.” PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as “opinions” without an adequate explanation of how the declaration fails to rebut the Examiner’s position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). As discussed herein, the PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no

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reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept the statements in Mr. Grimaldi's Declaration.

With respect to the arguments regarding Hu presented in response to the previous Office Action, the Examiner asserts that the arguments do not present any evidence that differences under 5 fold would be useful for diagnosis as asserted because PRO1864 is only overexpressed at 2 fold. As an initial matter, Applicants note that Applicants have stated that the nucleic acids identified as being differentially expressed in the semi-quantitative experiments of Example 18 were overexpressed at least 2 fold. This does not necessarily mean that the mRNA encoding PRO1864 was overexpressed 2 fold.

Furthermore, as previously noted, in Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of an antibody which binds to a polypeptide that is 2-fold or more differentially expressed in tumors to be used as a diagnostic.

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Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer or their corresponding proteins cannot serve as a molecular marker of cancer.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration previously submitted, establish that there is at least a two-fold difference in PRO1864 cDNA between melanoma and normal skin tissue. As Applicants explain below, it is more likely than not that the PRO1864 polypeptide is also differentially expressed and antibodies which bind to the PRO1864 polypeptide can be used to distinguish melanoma from normal skin tissue.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a **change** in the level of mRNA for a particular protein, generally leads to a corresponding **change** in the level of the encoded protein. Given Applicants' evidence of differential expression of the mRNA for the PRO1864 polypeptide in melanoma, it is likely that the PRO1864 polypeptide is differentially expressed and antibodies to proteins differentially expressed in certain tumors have utility as diagnostic and therapeutic tools.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (previously attached as Exhibit 1). As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast

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majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression.” Further, “the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment.” The references cited in the declaration and submitted therewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D. (previously attached as Exhibit 3), an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that “such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.” (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (previously submitted as Exhibit 4) and (4th ed. 2002) (previously submitted as Exhibit 5), Genes VI, (Benjamin Lewin, Genes VI (1997)) (previously submitted as Exhibit 6), Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004 (previously submitted as Exhibit 7) and Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002) (previously submitted as Exhibit 8).

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Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

The Examiner asserts that the second Grimaldi declaration states that it is unlikely that one identifies an increase or decrease in mRNA without an increase or decrease in the associated protein and that in the rare case where the protein does not correlate with mRNA this would still provide crucial information for the clinician. The Examiner asserts that he has cited numerous pieces of art that show mRNA does not correlate with protein and as such the instances in which there is no correlation are not as rare as indicated in the Declaration.

In particular, the Examiner asserts that the Alberts and Lewin references submitted by Applicants actually support the Examiner's position in that they teach that controls on several levels can have an effect on expression of the protein.

These arguments are not responsive. Applicants have already acknowledged that gene expression is regulated at numerous levels. However, as the supporting references and declarations Applicants have supplied make clear, regulation of mRNA levels is the predominant mechanism of control for the majority of genes.

With respect to Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (previously submitted as Exhibit 4, herein after Cell 3rd) and (4th ed. 2002) (previously submitted as Exhibit 5, herein after Cell 4th), as previously noted, Figure 9-2 of Cell 3rd shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Cell 3rd provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Cell 3rd at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Cell 3rd at 453 (emphasis added). Thus, as established in Cell 3rd, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

As previously noted, in Cell 4th, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that “a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA.*” Cell 4th at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Cell 4th illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, “the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes.” Cell 4th at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, “[f]or most genes transcriptional controls are paramount.” Cell 4th at 379 (emphasis added).

With respect to Lewin (previously submitted as Exhibit 6), as previously noted, Lewin states “having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription.” *Genes VI* at 847-848 (emphasis added). Thus, it is clear from Lewin that protein expression is predominantly regulated at the point of transcription initiation.

The Examiner also asserts that, while the art of Zhigang et al does show protein expression, the experiments were carried out to demonstrate this and, accordingly, this reference indicates that one needs to actually determine the expression of the protein in order to be sure of expression.

As previously noted, Zhigang reported that the correlation between mRNA expression and protein expression occurred in 93% of the samples tested. Applicants submit that there is no requirement to provide evidence sufficient to establish an asserted utility as a matter of statistical certainty. “Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.” M.P.E.P. at § 2107.02, part VII (2004) (emphasis in original, internal citations omitted). Accordingly, Applicants maintain that Zhigang is consistent with Applicants’ position that, in general, differential mRNA expression leads to differential expression of the encoded polypeptide.

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The Examiner cites Gokman-Polar as teaching the absence of any necessary correlation between increased mRNA levels and increased protein levels. In particular, the PTO relies on a statement from Gokman-Polar that "Quantitative reverse transcription-PCR analysis revealed that the PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isoenzyme expression is likely regulated at the posttranscriptional/translational level." Office Action at 5.

A close review of Gokman-Polar indicates that with one exception, the trend in the data is that mRNA and protein levels are positively correlated, supporting Applicants assertion that increased mRNA levels correlate with increased protein levels. In Figure 2, the protein level of two isozymes shows a decrease, while the third is increased. This same pattern is seen for the corresponding mRNA levels in Figure 6, although admittedly the increase in mRNA for the third isozyme is minimal. Similarly, comparing the protein levels of the three isozymes in Figure 4 to the corresponding mRNA levels in Figure 7, with one exception the mRNA levels are positively correlated to protein levels. While protein levels do not increase or decrease in direct proportion to the changes in mRNA, the trend in five of the six examples is that protein levels are positively correlated to mRNA levels. This evidence is hardly sufficient to establish that one of skill in the art would reasonably doubt that there is a reasonable correlation between mRNA levels and protein levels.

The Examiner cites Gygi as teaching that correlation between mRNA and protein levels were insufficient to predict protein expression and that those that were correlated suggested an importance of posttranslational mechanisms controlling gene expression. According to the Examiner Gygi teaches that simple deduction from mRNA analysis is insufficient.

As noted in the response to the previous Office Action, Gygi found that "there was a general trend of increased protein levels resulting from increased mRNA levels." Gygi p. 1726. However, it is important to note that Gygi did not look at whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Instead, Gygi considered whether the steady-state transcript level correlated with the steady-state level of the corresponding protein. Gygi discloses that similar mRNA levels for *different* genes did not universally result in equivalent protein levels for the *different* gene products, and similar protein levels for *different* gene products did not universally result from equivalent mRNA levels for the

different genes. These results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein.

Gygi has nothing to do with changes in protein levels resultant from changes in mRNA levels because they did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Thus, when Gygi asserts that protein levels cannot be accurately predicted from mRNA levels, this refers to the finding that cellular protein levels cannot always be calculated simply based on cellular mRNA levels. This is completely unrelated to the expectation of a change in protein levels as a function of the change in encoding mRNA levels. Gygi does not provide any insight whatsoever into the affects on protein levels caused by a change in the encoding mRNA levels. Applicants assert that increasing or decreasing the level of mRNA for the same gene leads to an increase or decrease for the corresponding protein. Since this issue is not addressed in Gygi, Gygi offers no support for the PTO's position.

With respect to the Polakis Declaration, the Examiner asserts that he has provided references showing that mRNA over-expression does not correlate with protein over-expression. The Examiner also asserts that, while the Declaration may show a correlation between mRNA and protein over-expression in some cases, no evidence has been submitted that it is the norm rather than the exception that protein levels parallel gene expression in cancer cells.

As discussed above, the references cited by the Examiner do not contravene Applicants' position that, in general, differential expression of mRNA leads to differential expression of the encoded polypeptide. Applicants submit that the declaration is based on personal knowledge of the relevant facts at issue. Dr. Polakis is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). As discussed herein, the PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Dr. Polakis based his analysis. Dr. Polakis has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has

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offered no reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept the statements in Dr. Polakis' Declaration.

The Examiner asserts that the Ashkenazi Declaration was not sufficient because there is no indication that PRO1864 protein levels increase or stay the same. According to the Examiner, further research would be required to determine PRO1864 protein levels in cancers showing gene amplification of PRO1864. The Examiner asserts that the asserted utility is not substantial as the real-world use has not been established and also is not specific because Applicant has not provided any objective evidence correlating the expression of the PRO1864 polypeptide with any particular disease-state.

As discussed above, Applicants maintain that the references cited by the Examiner do not contravene Applicants' position that, in general, differential expression of an mRNA leads to differential expression of the encoded polypeptide. With respect to the Examiner's assertion that Applicants have not provided evidence correlating the expression of the PRO1864 polypeptide with a particular disease state, Applicants submit that whether or not PRO1864 is the causative agent for melanoma does not impact its use as a diagnostic tool for melanoma. One does not need to know what the consequence of the differential expression is in order to exploit the differential expression to distinguish tumor from normal tissue.

In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (See the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polynucleotides. (See, e.g., U.S. Patent No. 6,204,371 and U.S. Patent No. 6,534,641, attached hereto as Exhibits 1 and 2.)

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason

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for one skilled in the art to question the objective truth of the statement of utility or its scope.” *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or “more likely than not” standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

[T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true “beyond a reasonable doubt.” **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence “that one of ordinary skill in the art would reasonably doubt the asserted utility.” *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references to establish “that one of ordinary skill in the art would reasonably doubt” that the disclosed polypeptide is differentially expressed in certain tumors and that the claimed antibodies can be used as diagnostic and therapeutic tools. Given the lack of support for the PTO’s position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants’ supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed antibodies can be used as diagnostic or therapeutic agents for cancer, particularly melanoma.

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Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies which bind to the PRO1864 polypeptide. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1864 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the mRNA for the PRO1864 polypeptide is more highly expressed in melanoma compared to normal skin tissue. These data are strong evidence that the PRO1864 gene and polypeptide are associated with melanoma. Thus, Applicants submit that they have provided evidence associating the PRO1864 gene and polypeptide with a specific disease. The asserted utility of the claimed antibodies as a diagnostic tool for cancer, particularly melanoma, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Conclusion

The PTO has challenged the reliability of the evidence reported in Example 18, and states that it provides no information regarding protein expression. The PTO also asserts that it has provided numerous references which demonstrate that mRNA does not correlate with protein.

Applicants have previously provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. Applicants maintain that the previously submitted second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The PTO has not offered any substantial reason or evidence to question these declarations and supporting references. One of skill in the art recognizes that antibodies which bind to polypeptides which are differentially expressed in certain cancers have utility as diagnostic or

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therapeutic tools for cancer. Applicants note that the claimed utility is specific because differential expression in melanoma is not a characteristic of proteins in general. Accordingly, antibodies in general cannot be used as diagnostic or therapeutic agents for melanoma.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic or therapeutic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a “reasonable” confirmation of a real world context of use. Applicants remind the PTO that:

A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Enablement

Claims 1-5 were rejected under 35 U.S.C. 112 on the assertion that, because the claimed invention is not supported by a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use it.

As discussed above, Applicants maintain that the claimed antibodies possess utility. Accordingly, those skilled in the art would know how to use them as diagnostic and therapeutic agents.

The Examiner asserts that he has supplied evidence for unpredictability in the art and countered the references and Declarations supplied. As discussed above, the references cited by

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the Examiner do not contravene Applicants position that, in general, differential mRNA expression leads to differential polypeptide expression.

The Examiner asserts that Pennica demonstrates that each gene amplification and correlation to protein overexpression needs to be determined by a case by case basis. According to the Examiner, the predictability of protein translation and its possible utility as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation.

As previously noted, the PTO is confusing the relationship between an increase in copy number of a gene or gene amplification on the one hand, and increased expression of a gene or mRNA expression on the other. Pennica provides that the *WISP-2* gene DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. (Pennica, page 14722) This result may not even be real, as the authors explain: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." Pennica at 14722 (emphasis added).

However, even if the lack of correlation between DNA copy number and mRNA level in Pennica is real, Pennica says nothing about a lack of correlation between the level of mRNA and the level of protein expression – Pennica did not even look at protein expression. It is the correlation between mRNA level, as assessed by probing the cDNA library, and the level of protein expression which is at issue here, not the correlation of gene copy number and mRNA levels. The data Applicants report in Example 18 indicate that there are more copies of the mRNA encoding the polypeptide of SEQ ID NO: 14 in melanoma than normal skin tissue. Nothing in Pennica is contrary to Applicants' assertion that it is well-established in the art that the level of protein is positively correlated to the level of mRNA.

As stated above, it is more likely than not that the polypeptide of SEQ ID NO: 14 is differentially expressed in melanoma. Even if Pennica supported the PTO's argument, which it does not, one contrary example does not establish that one of skill in the art would find it is more likely than not, that in general, there is no correlation between mRNA level and protein levels. In

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fact, as discussed above, the working hypothesis among those skilled in the art is that there is a direct correlation between mRNA levels and protein levels.

Conclusion

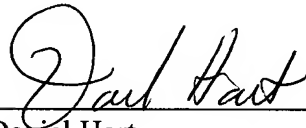
In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Sept. 2, 2005

By: 

Daniel Hart

Registration No. 40,637

Attorney of Record

Customer No. 30,313

(619) 235-8550

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